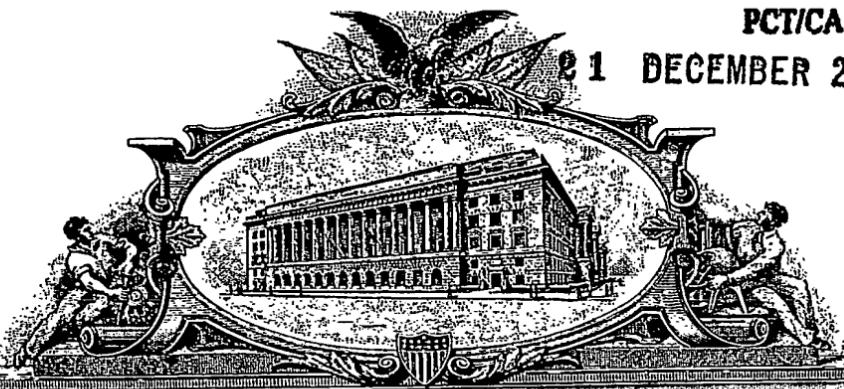


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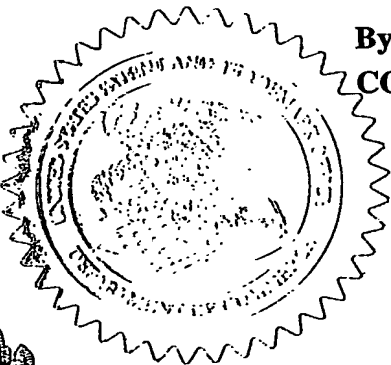
November 09, 2004

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7414 U.S. PTO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53(c).

Docket Number		50319/006001		Type a plus sign (+) inside this box -->	+
INVENTOR(S)/APPLICANT(S)					
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TITLE OF THE INVENTION (280 characters max)					
Methods and Compositions for use in Treating Diabetes					
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STATE	MA	ZIP CODE	02110-2214	COUNTRY	USA
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification		Number of pages: 14		<input checked="" type="checkbox"/> Cover Sheet: 1 page	
<input checked="" type="checkbox"/> Claims		Number of pages: 3		<input type="checkbox"/> Other (specify):	
<input checked="" type="checkbox"/> Abstract		Number of pages: 1			
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fees.			FILING FEE AMOUNT		\$80.00
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees not covered and apply any credits to Deposit Account Number: 03-2095					

22151 U.S. PTO
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102703

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

☒ Applicant claims small entity status under 37 C.F.R. § 1.27.

Respectfully submitted,

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DATE: October 27, 2003

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PROVISIONAL APPLICATION

UNDER 37 C.F.R. § 1.53(c)

APPLICANT: Francesco Bellini, Claude Vezeau, Gérard Ribes and Nicolas Chapal

TITLE: Methods and Compositions for Use in Treating Diabetes

METHODS AND COMPOSITIONS FOR USE IN TREATING DIABETES

5

Field of the Invention

This invention relates to methods and compositions for use in treating diabetes.

Background of the Invention

10 Diabetes mellitus is a disorder of carbohydrate metabolism, and develops when the body cannot effectively control blood glucose levels. The disease is characterized by inadequate secretion or utilization of insulin, high glucose levels in the blood and urine, and excessive thirst, hunger, weight loss, and urine production. It can lead to a number of serious complications, including cardiovascular disease, kidney disease, blindness, nerve damage, and limb ischemia.

15 Diabetes is divided into two types, 1 and 2, with the latter accounting for about 90% of cases. In type 1 diabetes, the body destroys the insulin-producing β cells of the pancreas, resulting in the inability of the body to produce insulin. Type 1 diabetes typically occurs in children or young adults, and generally is managed by insulin administration, strict diet, and exercise. Type 1 diabetes is observed as well in older adults following therapeutic failure of type

20 2 diabetes. Type 2 diabetes is characterized by impaired insulin secretion due to altered β cell function, as well as decreased ability of normally insulin sensitive tissues (e.g., the liver and muscle) to respond to insulin. Type 2 diabetes generally develops in those over 45, but is recently also being detected in younger people. The disease is associated with risk factors such as age, family history, obesity, lack of regular exercise, high blood pressure, and hyperlipidemia.

25 Treatment involves strict diet and exercise regimens, oral medications (e.g., medications that increase insulin secretion and/or insulin sensitivity), and, in some cases, insulin administration.

Type 2 diabetes is rapidly increasing in its importance as a major public health concern in the Western world. While one hundred years ago it was a relatively rare disease, today there are about 200 million type 2 diabetics worldwide, and this number is estimated to increase to greater

30 than about 300 million by the year 2025. This dramatic increase in the incidence of type 2 diabetes parallels an increase in the prevalence of obesity in Western cultures. Further, as more cultures adopt Western dietary habits, it is likely that type 2 diabetes will reach epidemic

proportions throughout the world. Given the seriousness of the complications associated with this disease, as well as its rapidly increasing incidence, the development of effective approaches to treatment is a primary concern in the field of medicine.

Summary of the Invention

The invention provides methods of treating diabetes (type 1 diabetes or type 2 diabetes) in patients, which involve administering to the patients a hydroxylated amino acid (for example, 4-hydroxyisoleucine, e.g., the 2S, 3R, 4S isomer of 4-hydroxyisoleucine) and one or more other antidiabetic agents, to obtain a synergistic effect. Examples of other antidiabetic agents that can be used in the invention include biguanides (e.g., metformin), sulfonylurea drugs, glinides, glitazones (e.g., thiazolidinediones, such as rosiglitazone maleate), glucagon-like peptide 1 receptor agonists (e.g., Exenatide®), and insulin. Other examples of antidiabetic (and other) agents that can be used in combination with hydroxylated amino acids according to the invention are listed below. The hydroxylated amino acid and other antidiabetic agents can be administered at or about the same time as one another or at different times. Also included in the invention are pharmaceutical kits and compositions (e.g., tablets or capsules) that include combinations of the agents noted above and elsewhere herein.

The invention provides several advantages. For example, because the drug combinations described herein are used to obtain synergistic effects, it is possible to consider administering less of each drug, leading to a decrease in the overall exposure of patients to drugs, as well as any untoward side effects of any of the drugs. In addition, greater control of the disease may be achieved, because the drugs can combat the disease through different mechanisms.

Other features and advantages of the invention will be apparent from the following detailed description and the claims.

Detailed Description of the Invention

The invention provides methods and pharmaceutical kits or compositions for use in treating diabetes. The invention is based on the administration of hydroxylated amino acids, such as 4-hydroxyisoleucine, to patients with one or more other antidiabetic agents, in order to obtain a synergistic effect.

As is discussed further below, examples of agents that can be administered with hydroxylated amino acids, such as 4-hydroxyisoleucine, according to the invention, include insulin, biguanides, sulfonylureas, glinides, glitazones, glucagon like peptide-1 (GLP-1) and agonists thereof, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, and other agents mentioned herein. The methods and compositions of the invention are described in further detail, as follows.

Hydroxylated Amino Acids

Central to the invention is the administration of one or more hydroxylated amino acids (e.g., mono-hydroxylated amino acids, poly-hydroxylated amino acids, or lactonic forms of such hydroxylated amino acids), in combination with one or more other antidiabetic agents, to patients. A specific example of a hydroxylated amino acid that can be used in the invention is 4-hydroxyisoleucine (e.g., the 2S, 3R, 4S isomer), which has been shown both to stimulate insulin secretion in a glucose dependent manner, and to decrease insulin resistance (see, e.g., U.S. Patent No. 5,470,879; WO 01/15689; Broca et al., Am. J. Physiol. 277:E617-E623, 1999; the teachings of each of which are incorporated herein by reference).

4-hydroxyisoleucine for use in the invention can be obtained, for example, by chemical synthetic methods. However, this compound is naturally present in high quantities in the seeds of the legume fenugreek (*Trigonella foenum-graecum L.*), from which it can be purified using methods such as those described in U.S. Patent No. 5,470,879, WO 97/32577, WO 01/72688, and Wang et al., Eur. J. Org. Chem. 834-839, 2002, the teachings of each of which are incorporated herein by reference. 4-hydroxyisoleucine is preferably administered orally, but also can be administered by other routes including, e.g., subcutaneous, intramuscular, and intravenous routes. As can be determined by those of skill in this art, the amount of hydroxylated amino acid administered may be decreased when administration is carried out in combination with the use of another antidiabetic agent, as described herein, to obtain a synergistic effect.

Examples of agents that can be administered in combination with a hydroxylated amino acid, such as 4-hydroxyisoleucine, according to the invention, are described further below.

Insulin

5 As is discussed above, type 2 diabetes is characterized by abnormalities in insulin secretion and by insulin resistance of major target tissues, such as muscle, liver, and adipose tissues. This disease has generally been treated by the use of oral antidiabetic agents, such as insulinotropic and insulin sensitizing agents. Type 1 diabetes is characterized by massive destruction of pancreatic β cells, resulting in drastic hypoinsulinemia. Thus, administration of
10 exogenous insulin is central to the treatment of this disease. Insulin resistance also occurs in type 1 diabetes but, in contrast to type 2 diabetes, insulin resistance in type 1 diabetes is not a primary phenomenon but, rather, is a secondary event that can often be reversed by adequate insulin therapy. However, sometimes glycemic control by insulin administration is difficult to achieve, and insulin doses need to be greatly increased. Further, hyperglycemia contributes to
15 impaired insulin action in such subjects.

The binding of insulin to its receptor initiates a signal transduction cascade involving the insulin receptor substrates IRS1, IRS2, etc. A major function of insulin receptor substrates is to activate phosphatidylinositol 3-kinase, which plays a central role in the insulin signaling pathway. Defects in the insulin receptor or in early insulin signaling elements can play an
20 important role in the development of insulin resistance. Indeed, in the case of type 1 diabetes patients with insulin resistance, cellular defects in target tissues have been found that include alterations in insulin binding and intracellular insulin signal transduction involving PI3-kinase activation.

As is discussed above, 4-hydroxyisoleucine is a drug that exhibits both insulinotropic and
25 insulin sensitizing activities. The insulin sensitizing activity of the drug is related to activation of PI3-kinase in muscle and liver. Thus, use of a hydroxylated amino acid (e.g., 4-hydroxyisoleucine) in combination with insulin therapy can lead to increased PI3-kinase activation and thus decreased insulin resistance. Use of hydroxylated amino acids in combination with insulin therapy can therefore enable the use of decreased doses of insulin. The
30 invention thus includes the use of hydroxylated amino acids, such as 4-hydroxyisoleucine, in the treatment of type 1 diabetes.

Further, the invention also includes approaches involving combining insulin and hydroxylated amino acid therapy with one or more additional therapeutic approaches, such as those described elsewhere herein (e.g., therapy involving the use of one or more biguanides, sulfonylureas, glinides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents).

Biguanides

Metformin (Glucophage®, Bristol-Myers Squibb Company, U.S.; Stagid®, Lipha Santé, Europe) is a biguanide compound that is widely used in the treatment of type 2 diabetes. It is the first line drug used in the treatment of obese patients (BMI>27), unless contraindicated by, e.g., impaired renal function. Metformin treatment results in decreased blood glucose levels by several different mechanisms, including reduced intestinal glucose absorption, reduced appetite, enhanced peripheral hepatic utilization (insulin sensitizing effect), and reduced hepatic output.

The invention includes combination therapy involving the use of a biguanide, such as metformin, with a hydroxylated amino acid, such as 4-hydroxyisoleucine. Also included in the invention are approaches involving the use of biguanides and hydroxylated amino acids (such as 4-hydroxyisoleucine) in combination with other antidiabetic therapies including, for example, those described elsewhere herein (e.g., therapy involving the use of insulin, sulfonylureas, glinides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents).

Sulfonylureas and Glinides

Failure to control meal-related glucose peaks is a key factor in the loss of glycemic control in type 2 diabetes. This failure in prandial glycemic control results from an immediate impaired secretory function of pancreatic β cells and from extrapancreatic defects in insulin sensitivity (i.e., insulin resistance). Sulfonylurea drugs, which generally are the first line treatment for non-obese type 2 patients (BMI<27), increase the amount of insulin produced by the pancreas, and thus help to compensate for the body's resistance to insulin. Specific examples of sulfonylurea drugs include gliclazide (Diamicon®), glibenclamide, glipizide (Glucotrol® and

Glucotrol XL®, Pfizer), glimepiride (Amaryl®, Aventis), chlorpropamide (e.g., Diabinese®, Pfizer), tolbutamide, and glyburide (e.g., Micronase®, Glynase®, and Diabeta®). As is discussed above, 4-hydroxyisoleucine has insulin stimulatory and insulin sensitizing effects. Thus, combining a hydroxylated amino acid, such as 4-hydroxyisoleucine, with a sulfonylurea drug can be used for meal control in type 2 diabetes.

5 Treatment with a combination of a hydroxylated amino acid (such as 4-hydroxyisoleucine) and a sulfonylurea drug can be supplemented with treatment employing one or more additional therapeutic agents, such as the antidiabetic agents described herein. For example, one or more of the following types of agents can be used in such combinations: insulin, 10 biguanides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents.

Similar to sulfonylureas, meglitinides (i.e., glinides) are drugs that also stimulate the pancreatic β cells to release insulin. As a specific example, repaglinide (Prandin® or 15 NovoNorm®; Novo Nordisk) acts by closing potassium-ATP channels of pancreatic β cells, which results in depolarization of the cell membrane, leading to calcium influx, which in turn triggers insulin secretion. It is fast and short acting, making it a useful pre-meal treatment. Examples of meglitinide drugs in addition to repaglinide that can be used in the invention include ormitiglinide, nateglinide, senaglinide, and BTS-67582, which can each be taken before 20 meals (also see WO 97/26265, WO 99/03861, and WO 00/37474). Nateglinide (Starlix) may be particularly useful in reducing post-prandial blood glucose excursions, as it improves first phase insulin secretion.

Treatment with a combination of a hydroxylated amino acid (such as 4-hydroxyisoleucine) and a glinide can be supplemented with treatment employing any 25 combination of the following agents: insulin, biguanides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents.

Insulin Sensitizing Agents

As is discussed above, increased levels of glucose and lipids in the blood are fundamental characteristics of diabetes. The resulting glucotoxicity and lipotoxicity can lead to altered β cell function. Glitazones, such as thiazolidinediones, are insulin sensitizing agents and also are effective in reducing free fatty acid and triglyceride concentrations in the blood. As is noted above, 4-hydroxyisoleucine has glucose-dependent insulintropic activity, as well as extrapancreatic insulin-sensitizing effects. Thus, treatment using a combination of a thiazolidinedione and a hydroxylated amino acid, such as 4-hydroxyisoleucine, has beneficial effects on both glucotoxicity and lipotoxicity.

One example of a thiazolidinedione that can be used in the invention is rosiglitazone maleate (Avandia®, Glaxo Smith Kline). Another example is pioglitazone (Actos®, Eli Lilly, Takeda). Additional examples of thiazolidinedione drugs that can be used in the invention include troglitazone, ciglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037, T 174, and the compounds disclosed in WO 97/41097 (DRF-2344), WO 97/41119, WO 97/41120, WO 98/45292, and WO 00/41121, the contents of each of which are incorporated herein by reference.

Treatment involving the combined use of a hydroxylated amino acid, such as 4-hydroxyisoleucine, and thiazolidinediones, such as rosiglitazone, can also include other agents, such as insulin, biguanides, sulfonylureas, glinides, other insulin sensitizing agents, GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents.

Additional examples of insulin sensitizing agents that can be used in combination with a hydroxylated amino acid, according to the invention, include GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516, and the compounds described in WO 99/19313 (NN622/DRF-2725), WO 00/23415, WO 00/23416, WO 00/23417, WO 00/23425, WO 00/23445, WO 00/23451, WO 00/50414, WO 00/63153, WO 00/63189, WO 00/63190, WO 00/63191, WO 00/63192, WO 00/63193, WO 00/63196, and WO 00/63209, the contents of each of which are incorporated herein by reference.

Glucagon Like Peptide-1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1) is a potent stimulator of glucose-dependent insulin secretion via a cyclic AMP-mediated mechanism in pancreatic β cells. Exendin-4 (1-39) (Ex-4), which is isolated from Gila monster venom, is a highly specific GLP-1 receptor agonist that exhibits a prolonged duration of insulinotropic action. Exenatide® (AC2993; Amylin Pharmaceuticals) is a synthetic version of Ex-4, and has been shown to improve glycemic control by multiple actions, including glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, slowed gastric emptying, decreased food intake, and reduced weight. Ex-4 has also been reported to increase insulin sensitivity via a PI3 kinase-dependent mechanism. A sustained release formulation (i.e., Exenatide LAR®; Amylin Pharmaceuticals) can also be used. Other examples of GLP-1 agonists that can be used in the invention are described in WO 98/08871 and WO 00/42026, the contents of each of which are incorporated herein by reference.

Treatment involving the combined use of hydroxylated amino acids, such as 4-hydroxyisoleucine, and a glucagon-like peptide 1 receptor agonist, such as Exenatide®, can also include the use of other antidiabetic agents, such as insulin, biguanides, sulfonylureas, glinides, insulin sensitizing agents (e.g., glitazones), agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, glucokinase activators, and other agents.

Agents that Slow Down Carbohydrate Absorption

Agents that slow down carbohydrate absorption can be used to control post-prandial glucose levels. One example of this type of agent is α -glucosidase inhibitors, which act by blocking the breakdown of oligo and disaccharides from dietary carbohydrates, thus slowing down the absorption of glucose. Examples of α -glucosidase inhibitors include acarbose, miglitol, voglibose, and emiglitate.

Other agents that slow down carbohydrate absorption are those that inhibit gastric emptying. In particular, there are a number of hormones that are known to inhibit gastric emptying, including glucagon like peptide-1, cholecystokinin, and also amylin, which is synthesized and secreted from pancreatic β cells. A synthetic amylin analogue (pramlintide) has been developed for the treatment of diabetes. Use of a combination of a hydroxylated amino acid, such as 4-hydroxyisoleucine, which has insulinotropic and insulin sensitizing properties,

and agents slowing down carbohydrate absorption, can be carried out to achieve synergistic effects in post-prandial glucose control.

Treatment involving the combined use of hydroxylated amino acids, such as 4-hydroxyisoleucine, and agents that slow down carbohydrate absorption, as described herein, can also include the use of other antidiabetic agents, such as insulin, biguanides, sulfonylureas, 5 glinides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, glucagon antagonists, glucokinase activators, and other agents.

Glucagon Antagonists

10 Glucagon is a hormone that acts in conjunction with insulin to regulate the levels of glucose in the blood. It acts primarily by stimulating cells, such as liver cells, to release glucose when blood glucose levels fall. Thus, to decrease the levels of glucose in the blood in diabetic patients, it is useful to administer glucagon antagonists which, according to the invention, can be administered with a hydroxylated amino acid, such as 4-hydroxyisoleucine.

15 Examples of glucagon antagonists that can be used in the invention include quinoxaline derivatives (e.g., 2-styryl-3-[3-(dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline; Collins et al., Bioorganic and Medicinal Chemistry Letters 2(9):915-918, 1992); skyrin and skyrin analogues (see, e.g., WO 94/14426), 1-phenyl pyrazole derivatives (U.S. Patent No. 4,359,474); substituted disilacyclohexanes (U.S. Patent No. 4,374,130), substituted pyridines and 20 biphenyls (WO 98/04528); substituted pyridyl pyrroles (U.S. Patent No. 5,776,954); 2,4-diaryl-5-pyridylimidazoles (WO 98/21957, WO 98/22108, WO 98/22109, and U.S. Patent No. 5,880,139); 2,5-substituted aryl pyrroles (WO 97/16442 and U.S. Patent No. 5,837,719); substituted pyrimidinone, pyridone, and pyrimidine compounds (WO 98/24780, WO 98/24782, WO 99/24404, and WO 99/32448); 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanones (Madsen et al., J. Med. Chem. 41:5151-5157, 1998); alkylidene hydrazides (WO 25 99/01423 and WO 00/39088); and other compounds such as those described in, e.g., WO 00/69810, WO 02/00612, WO 02/40444, WO 02/40445, and WO 02/40446. In addition, further glucagon antagonists can be identified using, e.g., the methods described in U.S. Patent Application Publication US 2003/0138416 A1, the teachings of which are incorporated herein by 30 reference.

Treatment involving the combined use of hydroxylated amino acids, such as 4-hydroxyisoleucine, and a glucagon antagonist, such as those referred to above, can also include the use of other antidiabetic agents, such as insulin, biguanides, sulfonylureas, glinides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucokinase activators, and other agents.

Glucokinase Activators

Glucokinase is an enzyme that plays a central role in glycolysis, glucose uptake, and glycogen synthesis. Activators of glucokinase have been proposed for use in treating diabetes. Examples of such compounds can be found, for example, in WO 00/58293, WO 01/44216, WO 01/83465, WO 01/83478, WO 01/85706, or WO 01/85707, the contents of each of which are incorporated herein by reference. In addition, further glucokinase activators can be identified using, e.g., the methods described in U.S. Patent Application Publication US 2003/0138416 A1.

Glucokinase activators can be administered with hydroxylated amino acids, such as 4-hydroxyisoleucine, according to the invention, using standard methods. Further, treatment involving the combined use of hydroxylated amino acids, such as 4-hydroxyisoleucine, and glucokinase activators, such as those described in the documents referred to above, can also include the use of other antidiabetic agents, such as insulin, biguanides, sulfonylureas, glinides, insulin sensitizing agents (e.g., glitazones), GLP-1 receptor agonists, agents that slow carbohydrate absorption (e.g., acarbose), glucagon antagonists, and other agents.

Other Agents

Examples of other antidiabetic agents that can be used in combination with a hydroxylated amino acid, such as 4-hydroxyisoleucine (as well as other agents described herein), according to the invention include imidazolines (e.g., efaroxan, idazoxan, phentolamine, and 1-phenyl-2-(imidazolin-2-yl)benzimidazole); glycogen phosphorylase inhibitors (see, e.g., WO 97/09040); oxadiazolidinediones, dipeptidyl peptidase-IV (DPP-IV) inhibitors, protein tyrosine phosphatase (PTPase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 (GSK-3) inhibitors, compounds that modify lipid metabolism (e.g., antihyperlipidemic agents

and antilipidemic agents), peroxisome proliferator-activated receptor (PPAR) agonists, and retinoid X receptor (RXR) agonists (e.g., ALRT-268, LG-1268, and LG-1069).

Hyperlipidemia is a primary risk factor for cardiovascular disease, which is particularly prevalent among diabetic patients. Thus, hydroxylated amino acids, such as 4-hydroxyisoleucine, can also be administered, according to the invention, in conjunction with antihyperlipidemic agents or antilipidemic agents (e.g., cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol, and dextrothyroxine), optionally, in combination with other agents described herein.

Further, hydroxylated amino acids, such as 4-hydroxyisoleucine, can also be administered, according to the invention, in conjunction with one or more antihypertensive agents (optionally, in combination with other agents described herein), as hypertension has been found to be associated with altered blood insulin levels. Examples of antihypertensive agents that can be used in the invention include β -blockers (e.g., alprenolol, atenolol, timolol, pindolol, propranolol, and metoprolol), angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, and ramipril), calcium channel blockers (e.g., nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem, and verapamil), and α -blockers (e.g., doxazosin, urapidil, prazosin, and terazosin).

Administration

The pharmaceutical agents described herein can be administered separately (e.g., as two pills administered at or about the same time), which may be convenient in the case of drugs that are already commercially available in individual forms. Alternatively, for drug combinations that can be taken at the same time, by the same route (e.g., orally), the drugs can be conveniently formulated to be within the same delivery vehicle (e.g., a tablet, capsule, or other pill). Methods for formulating drugs that can be used in the invention are well known in the art and are described, for example, in Remington: The Science and Practice of Pharmacy (20th edn., A.R. Gennaro, ed.), Lippincott Williams & Wilkins, 2000. These methods include the use of, e.g., capsules, tablets, aerosols, solutions, suspensions, and preparations for topical administration.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients can be, for example, inert diluents or fillers (e.g., sucrose and sorbitol), lubricating agents, glidants, and antiadhesives

(e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, and talc). Formulations for oral use can also be provided as chewable tablets, or as hard gelatin capsules in which the active ingredient(s) is mixed with an inert solid diluent, or as soft gelatin capsules in which the active ingredient(s) is mixed with water or an oil medium. Formulations for parenteral administration can contain, for example, excipients, sterile water, or saline; polyalkylene glycols such as polyethylene glycol; oils of vegetable origin; or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Nanoparticulate formulations (e.g., biodegradable nanoparticles, solid lipid nanoparticles, and liposomes) can be used to control the biodistribution of the compounds.

The concentrations of the agents in the formulations will vary, depending on a number of factors including the dosages of the agents to be administered, the route of administration, the nature of the agent, the frequency and mode of administration, the therapy desired, the form in which the agents are administered, the potency of the agents, the sex, age, weight, and general condition of the subject to be treated, the nature and severity of the condition treated, any concomitant diseases to be treated, and other factors that will be apparent to those of skill in the art.

Generally, in the treatment of adult humans, dosages from about 0.001 mg to about 1000 mg (e.g., about 0.05-500, 0.1-250, 0.5-100, 1-50, or 2-25 mg) of each active compound per kg body weight per day can be used. A typical oral dosage can be, for example, in the range of from about 0.001 mg to about 100 mg (e.g., about 0.01-50 or 0.05-10 mg) per kg body weight per day, administered in one or more dosages, such as 1 to 3 dosages. Dosages can be increased or decreased as needed, as can readily be determined by those of skill in the art. For example, the amount of a particular agent can be decreased when used in combination with another agent, if determined to be appropriate. In addition, reference can be made to standard amounts and approaches that are used to administer the agents mentioned herein. Examples of dosages for drugs mentioned herein are provided in Table 1, below. The drugs can be used in these dosages when combined with a hydroxylated amino acid (e.g., 4-hydroxyisoleucine), which generally is administered in an amount in the range of, for example, 250 mg - 1 g/day (e.g., 350-900, 450-800, or 550-700 mg/day). Alternatively, due to the synergistic effects obtained when using drug combinations of the invention, the amounts in Table 1 and/or the amount of hydroxylated amino

acid administered can be decreased (by, e.g., about 10-70%, 20-60%, 30-50%, or 35-45%), as determined to be appropriate by those of skill in this art.

Table 1

Drug substance	Dosage and/or administration
Insulin	400 IU per vial - 40 IU per day (mean value)
Gliclazide (Diamicon)	80 mg/tablet - 1 to 4 tab. per day
Glibenclamide (Daonil) or Glyburide (Micronase, Glynase, Diabeta)	5 mg/tablet - 1 to 3 tab. per day (Glibenclamide); 1.25 to 6 mg/tablet - 1 to 2 tab. per day (Glyburide)
Glipizide (Glucotrol, Glibenese)	5 mg/tablet - 1 to 4 tab. per day
Glimepiride (Amaryl, Amarel)	1 to 4 mg/tablet - 6 mg. per day maximum
Chlorpropamide (Diabinese)	250 mg/tablet - 125 to 1000 mg per day per day
Tolbutamide	500 mg/tablet - 1 to 4 tab. per day
Repaglinide (Prandin)	0.5 to 16 mg per day
Nateglinide, Senaglinide(Starlix)	60 to 120 mg/tablet - 3 tab. per day
Tolazamide	100 to 500 mg / tablet
Rosiglitazone	2 to 8 mg / tablet - 8 mg per day maximum
Pioglitazone	15 to 45 mg / tablet - 15 to 45 mg per day
Troglitazone	200 to 400 mg / tablet - 200 to 600 mg per day
Ciglitazone	0.1 mg/ tablet
Exetanide (Amylin)	0.09 to 0.270 mg per day
Acarbose	50 to 100 mg/tablet - 150 to 600 mg. per day
Miglitol	50 to 100 mg/tablet - 150 to 300 mg. per day
Voglibose	0.1 to 0.9 mg per day
Phentolamine	50 mg 4 to 6 times per day
Cholestyramine (Colestipol)	4g /unit - 12 to 16 g per day
Clofibrate	500 mg/capsule - 1 to 4 caps/day per day
Gemfibrozil Lipur)	450 mg / tablet - 2 tab. per day
Lovastatin	10 and 20 mg / tablet
Pravastatin	20 mg/tablet - 10 to 40 mg per day
Simvastatin (Zocor , Lodaless)	5 and 20 mg / tablet - 5 to 40 mg per day
Probucol	250 mg / tablet - 1g per day
Dextrothyroxine	2 to 6 mg per day
Alprenolol	50 mg / tablet - 4 to 8 tab per day
Atenolol	50 to 100 mg / tablet - 100 to 200 mg per day
Timolol	10 mg / tablet - 10 to 20 mg per day
Pindolol	5 and 15 mg / tablet - 5 to 60 mg per day
Propranolol	40 mg / tablet - 80 to 160 mg per day
Metoprolol	100 and 200 mg / tablet - 50 to 200 mg per day
Captopril	25 and 50 mg /tablet - 12.5 to 150 mg per day
Enalapril	5 and 20 mg / tablet - 5 to 40 mg per day
Nifedipine	10 mg / capsule - 30 to 60 mg per day
Diltiazem	60 mg/tablet - 3 to 6 tab. per day
Verapamil	120 and 240 mg / capsule - 240 to 360 mg per day
Doxazosin	2 to 8 mg per day
Prazosin	2.5 and 5 mg/ tablet - 2.5 to 20 mg per day

The invention also provides pharmaceutical compositions including the drug combinations noted above. The drugs can be formulated together in an appropriate form, for example, in a tablet or a capsule. Also included in the invention are kits that include the drug combinations in separate formulations, but with instructions to use them together.

5 All publications cited above are incorporated herein by reference in their entirety. Other embodiments are within the following claims.

What is claimed is:

1. A method of treating diabetes in a patient, said method comprising administering to the patient a hydroxylated amino acid and a second antidiabetic agent.

2. The method of claim 1, wherein said hydroxylated amino acid is 4-hydroxyisoleucine.

3. The method of claim 2, wherein said 4-hydroxyisoleucine is the 2S, 3R, 4S isomer of 4-hydroxyisoleucine.

4. The method of claim 1, wherein said second antidiabetic agent is insulin.

5. The method of claim 1, wherein said second antidiabetic agent is a biguanide.

6. The method of claim 5, wherein said biguanide is metformin.

7. The method of claim 1, wherein said second antidiabetic agent is a sulfonylurea drug.

8. The method of claim 1, wherein said second antidiabetic agent is a glinide.

9. The method of claim 1, wherein said second antidiabetic agent is a thiazolidinedione.

10. The method of claim 9, wherein said thiazolidinedione is rosiglitazone maleate or pioglitazone.

11. The method of claim 1, wherein said second antidiabetic agent is a glucagon-like peptide 1 receptor agonist.

12. The method of claim 11, wherein said glucagon-like peptide 1 receptor agonist is Exenatide®.

13. The method of claim 1, wherein said hydroxylated amino acid is administered to said patient at or about the same time as said second antidiabetic agent.

14. The method of claim 1, wherein said diabetes is type 2 diabetes.

15. A pharmaceutical kit comprising a hydroxylated amino acid and a second
5 antidiabetic agent.

16. The pharmaceutical kit of claim 15, wherein said hydroxylated amino acid is 4-
hydroxyisoleucine.

10 17. The pharmaceutical kit of claim 16, wherein said 4-hydroxyisoleucine is the 2S, 3R,
4S isomer of 4-hydroxyisoleucine.

18. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is insulin.

15 19. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is a
biguanide.

20. The pharmaceutical kit of claim 19, wherein said biguanide is metformin.

20 21. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is a
sulfonylurea drug.

22. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is a
glinide.

25 23. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is a
thiazolidinedione.

24. The pharmaceutical kit of claim 23, wherein said thiazolidinedione is rosiglitazone
30 maleate or pioglitazone.

25. The pharmaceutical kit of claim 15, wherein said second antidiabetic agent is a glucagon-like peptide 1 receptor agonist.

5 26. The pharmaceutical kit of claim 25, wherein said glucagon-like peptide 1 receptor agonist is Exenatide®.

27. The pharmaceutical kit of claim 15, wherein said hydroxylated amino acid and said second antidiabetic agent are formulated into a single composition.

10 28. The pharmaceutical kit of claim 27, wherein said single composition is a tablet or a capsule.

METHODS AND COMPOSITIONS FOR USE IN TREATING DIABETES

Abstract of the Disclosure

This invention relates to methods and compositions for treating diabetes, which involve
5 the use of hydroxylated amino acids, such as 4-hydroxyisoleucine, and one or more other
antidiabetic agents.

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